

Motoric Signs of CNS Dysfunction Associated With Alcohol and Cocaine Withdrawal

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Received January 28, 1992; first revised version received November 11, 1992; second revised version received January 28, 1993; accepted February 18, 1993.

Abstract. Measures of hand tremor and body sway were recorded from 6 alcohol-dependent (AD) and 16 cocaine-dependent (CD) patients after 1, 3, and 12 weeks of verified abstinence. The same measures were recorded from 15 nonpatient control subjects after comparable intervals. Hand tremor was transduced via an accelerometer. Body sway was transduced by a force-sensitive platform. Analyses revealed different patterns of motoric dysfunction in the AD and CD groups. AD patients exhibited enhanced hand tremor during a pointing task and enhanced body sway. Both of these abnormalities remitted with continued abstinence. CD patients exhibited enhanced and unchanging levels of resting tremor across the first 12 weeks of abstinence, but they had normal levels of body sway and action tremor. These results are interpreted as reflecting a subclinical cerebellar dysfunction in recovering AD patients, and a subclinical extrapyramidal dysfunction in the CD counterparts.

Key Words. Alcohol dependence, drug dependence, tremor, static ataxia, movement disorder.

Case reports and anecdotes have long suggested a correlation between chronic alcohol abuse and a variety of movement disorders. Postural tremors of the limbs (Carrie, 1965; Koller et al., 1985) and disturbances in gait and standing steadiness (Skillicorn, 1958; Victor et al., 1959; Silvuerskiold, 1977) are perhaps the most frequently reported correlates. However, reports of choreiform and athetoid-like movements have also appeared in the literature (Nieman et al., 1990). These findings have often been interpreted as reflecting alcohol-induced effects. Unfortunately, most studies of movement disorders in chronic alcohol abusers have been of the case report type and are incapable of determining the reliability of any hypothesized association. The few studies that are capable of this determination have produced variable results. There are several possible reasons: (1) There is variability across studies with regard to the prevalence of confounding medical and psychiatric disorders (such as head injury, seizure disorder, epilepsy, schizophrenia, and depression) or other drug use in the alcohol-abusing group. The neglect of such potential confounding factors effectively negates the ability to draw a causal link

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between alcohol abuse and movement disorder. (2) Variability in findings has been introduced by the use of arbitrary methods, both in the diagnosis of alcohol abuse/dependence and in the assessment of motor dysfunction. Reliable and sensitive methods are available in both areas. (3) Variability has been introduced when investigators fail to consider the effects of duration of abstinence and prescribed medications. Obviously, both of these variables could influence the magnitude of an alcohol-induced movement disorder and the likelihood of detecting its presence.

The present study was designed to address all of these issues. It focused on a group of uncomplicated alcohol-dependent patients, free of neurological and psychiatric complications and other substance abuse disorders. The present study also used standardized methods for psychiatric diagnosis and objective, quantitative methods for the detection of movement disorders. Assessments of motor function were made after precisely specified intervals of abstinence from alcohol and all other drugs.

In addition to evaluating movement disorders in chronic alcohol abusers, the present study also evaluated movement disorders in a group of age- and education-matched cocaine abusers. The justification for studying these patients comes from a variety of sources. Volkow et al. (1988) reported reduced prefrontal and cerebellar blood flow in 3-day abstinent cocaine abusers who were studied with positron emission tomography (PET). A subsequent study by Volkow et al. (1991) found abnormal glucose utilization within the basal ganglia of a similar group of patients. In addition to the PET studies, there have been several case reports suggesting the existence of Parkinsonian-like movement disorders in an analogous population, recovering amphetamine abusers (Lundh and Tunving, 1981). Collectively, these findings justify a more intensive examination of movement disorders in recovering cocaine abusers.

Methods

Subjects. Alcohol- or cocaine-dependent patients were recruited during their initial week of inpatient hospitalization for substance abuse treatment. Drug-naïve control subjects were recruited through newspaper advertisements. All subjects signed an informed consent agreement before any questionnaires, interviews, or tests were administered. They were paid for their time.

Patients with admitting diagnoses of either alcohol or cocaine dependence were contacted by a research assistant. At that time, preliminary information was obtained about the patient's demographic characteristics, drug and alcohol use, and medical and psychiatric history. This information was supplemented by data from the medical chart. Patients with histories of neurological disorders, major head injuries (loss of consciousness > 10 minutes), epilepsy, seizures (including drug-related seizures), cardiovascular or liver disease, or disorders affecting the integrity of the limbs were excluded from further consideration. Patients receiving psychoactive medications were also excluded. Those who met inclusionary criteria at this first stage were scheduled for the laboratory evaluation. A structured diagnostic interview, using the Diagnostic Interview Schedule (Robins et al., 1981) and the substance abuse section of the Structured Clinical Interview for *DSM-III-R* (Spitzer et al., 1987), was administered by a research assistant 2 weeks later, after the symptoms of acute withdrawal had subsided. This interview was used to confirm the presence of a *DSM-III-R* diagnosis of cocaine or alcohol dependence and the absence of major psychiatric (i.e., Axis I) disorders. The interview was tape-recorded and monitored by a clinician to ensure reliability and validity of the diagnosis.

Other questionnaires (available by request) were used to collect additional information about demographic characteristics, licit and illicit drug use, and family history of schizophrenia or drug abuse.

Control subjects were invited to contact a research assistant by telephone. At that time, a brief interview was conducted, and potential candidates were invited to visit the Health Center for a more extensive evaluation. This evaluation used the same interview procedures and exclusionary criteria outlined above. None of the subjects in the control group met diagnostic criteria for any drug abuse/dependence category (except nicotine).

Table 1 presents the characteristics of the three subject groups. The three groups were comparable in age. Obviously, the two patient groups were quite different from the control subjects and from each other in their drug-use habits. None of the 16 subjects in the cocaine-dependent category met criteria for alcohol or opiate dependence, though four met criteria for alcohol abuse. None had a history of intravenous cocaine use. Smoking was the predominant route of administration. The six subjects in the alcohol-dependent group were not regular users of either cocaine or opiates. Both patient groups may be characterized as having a history of moderate to severe dependence over a period of < 5 years, without major medical complications.

Table 1. Demographic characteristics

	Groups		
	Cocaine	Alcohol	Control
Age (yr)	30.7 (2.3)	34.1 (1.8)	32.3 (1.2)
Gender (M/F)	16/0	6/0	15/0
Race (B/H/C)	6/4/6	3/2/1	4/2/9
# Days preceding month			
Used cocaine	18 (2.3) ¹	0 (0)	0 (0)
Used alcohol	14 (5.5)	28 (2.2) ¹	17 (2.5)
Average amount used/occasion			
Cocaine (g)	0.7 (0.2) ¹	0 (0)	0 (0)
Alcohol (# standard drinks)	6 (1.5)	13 (2.4)	3 (1.1)
# Previous treatments for substance abuse	0.9 (0.1) ¹	2 (0.2) ¹	0 (0)

Note. Standard deviations are in parentheses.

1. Significantly different from normal control, $p < 0.05$.

Procedure. Patients were tested 7-10, 16-20, and 94-100 days after their last use of cocaine or alcohol. Normal control subjects were tested after equivalent delays. When patients were no longer hospitalized, they visited the hospital on one randomly chosen day each week for toxicological analysis of urine and breath samples. To discourage surreptitious use, < 48 hours' notice was provided for this appointment. Patients ($n = 6$) who tested positive for cocaine or alcohol on any occasion were dropped from the study. Control subjects were not required to submit regular urine or breath samples. Urine and breath samples were collected from these subjects only on the days of testing.

On the afternoon of each experimental day, the subject was escorted into the laboratory. He was instructed to remove his shoes and stand on a metal platform (Anima Gravicorder Model 4301). Six 6.4-second trials were then conducted, during which the subject tried to balance his weight over his dominant foot. The first trial was considered practice and discarded. During the subsequent five trials, the analogue outputs of the balance platform, representing anterior/posterior and lateral sway, were digitized at a rate of 40 Hz for 6.4 seconds. These digitized signals were submitted to a fast Fourier transform, and a score representing total signal power from 0.156 to 9.98 Hz was calculated. The scores for anterior/posterior and lateral sway were collapsed and summed across trials.

Hand tremor was transduced by a Grass Instrument Company Model SPA1 single plane accelerometer, which was taped to the index finger of the subject's nondominant hand. With the subject seated and at rest for 2 minutes, and with his hand in a supine position, the accelerometer was oriented in the vertical plane. Before the pointing task (described below), the orientation of the accelerometer was switched to the horizontal. The output of the accelerometer was digitized at a rate of 100 Hz and processed by a fast Fourier transform. Signal power (i.e., tremor amplitude) was calculated in 0.78-Hz bands.

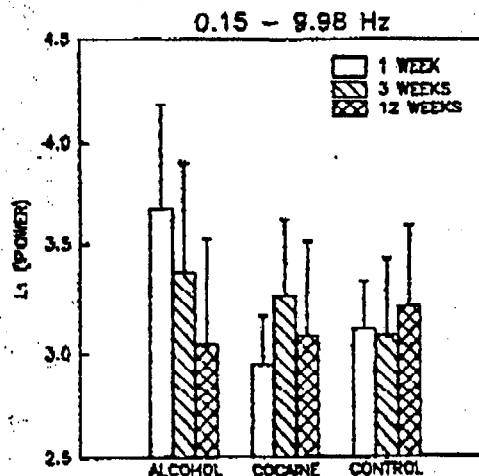
During the pointing task, the subject was required to keep his nondominant arm in an outstretched posture. Light-emitting diodes (LEDs), situated at eye level 0° and 30° off the vertical plane, were alternatively illuminated every 10 seconds over a 100-second period. The subject was instructed to move his hand rapidly to follow the apparent movement of the LEDs. He was instructed to maintain a pointing posture toward this target until the alternate LED was illuminated. The amount of action tremor occurring within this context was estimated by the power spectral density (PSD) of the accelerometer signal during the first 1.28 seconds of each trial (i.e., after LED onset). PSDs were averaged across the 10 trials.

Results

Body sway and tremor (resting and action) were converted to their natural logarithmic equivalents before analysis. Body sway, which was represented by a single score, was analyzed by two-factor analyses of variance (ANOVAs). Group (cocaine dependent/alcohol dependent/normal control) was the between-subjects factor, and session (1 week/3 weeks/12 weeks) was the within-subject factor. The analyses of resting and action tremor included frequency bin as an additional within-subjects factor. Where appropriate, the degrees of freedom for these analyses were reduced using the Geisser-Greenhouse method (Geisser and Greenhouse, 1958). Significance was assumed at p values of < 0.05 .

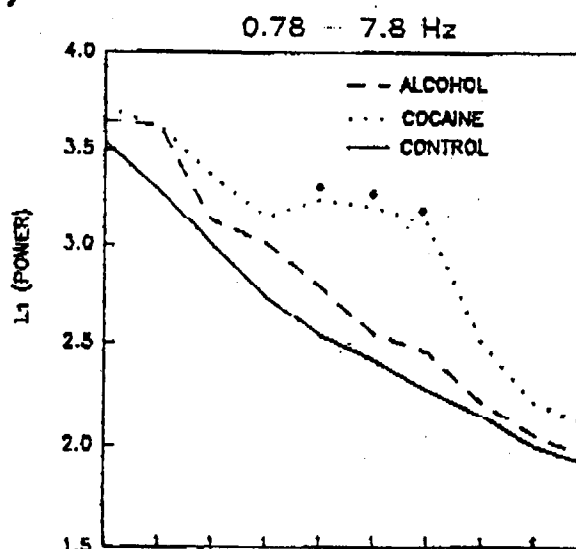
The ANOVA of body sway scores revealed no main effects of either patient group or session. However, the group $\times$ session interaction was significant ($F = 4.52$; $df = 3.9, 41.2$; $p < 0.005$). Post hoc analyses (Sheffé, $p < 0.05$) revealed that alcohol-dependent patients exhibited more body sway than the other two groups, but at only the first time point, i.e., after 7-10 days of abstinence (Fig. 1).

Fig. 1. Body sway ($\ln(\text{power}) + 1 \text{ SD}$) plotted as a function of group and time



Estimates of normal physiologic tremor and abnormal tremor were obtained by calculating the power-spectral density of tremor in two separate frequency bands (Young, 1984). ANOVAs of normal physiologic tremor (7.8-9.36 Hz) revealed no significant differences among the groups. However, ANOVAs of tremor in the abnormal frequency range (0.78-7.8 Hz) revealed several interesting group differences. During the resting condition, for example, hand tremor was of significantly larger amplitude in the cocaine-dependent group than in the other groups (Fig. 2). The group difference in resting tremor was restricted to a frequency

Fig. 2. Rest tremor amplitude (ln(power)) at rest as a function of group and frequency



Asterisks designate frequencies at which cocaine-dependent patients differ from the two other groups (Scheffé, $p < 0.05$).

range of 3.9 to 5.46 Hz (group $\times$ frequency bin: $F = 1.96$; $df = 3.7, 38.8$; $p < 0.05$) and did not diminish with continued abstinence (Fig. 3). Scheffé post hoc tests confirmed this interpretation.

By contrast, hand tremor recorded during the pointing task was significantly elevated in the alcohol-dependent group but not in the cocaine-dependent group. This difference was restricted to a frequency range of 0.15 to 0.93 Hz and did diminish with continued abstinence (group $\times$ session $\times$ frequency bin: $F = 2.3$; $df = 8.6, 90.3$; $p < 0.04$). By the third laboratory session (i.e., after 12 weeks of abstinence), the elevated action tremor in the alcohol-dependent group had disappeared. Figs. 4 and 5 illustrate these data.

Discussion

The present study revealed significant differences between groups of alcohol-dependent patients, cocaine-dependent patients, and age-matched normal control subjects on several objective indices of body sway and hand tremor. The differences

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between the alcohol-dependent and control groups disappeared over time. After 1-3 weeks of abstinence, the alcohol-dependent group no longer differed from the control group on an index of body sway. The elevated action tremor found in the alcohol-dependent group was more long lasting, but nonetheless remitted after 12 weeks of abstinence. The only significant difference found between the cocaine-dependent group and the control group pertained to resting tremor, which did not diminish with continued abstinence, at least over the period of time studied.

The pattern of differences found in the alcohol-dependent group obviously suggests the presence of cerebellar dysfunction. This hypothesis is certainly not new

Fig. 3. Average rest tremor amplitude from 3.9 to 5.46 Hz plotted as a function of group and time

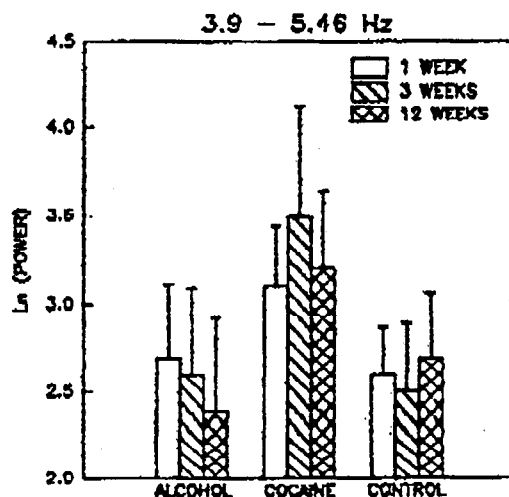


Fig. 4. Action tremor amplitude (Ln(power)) during pointing task (session 1 only) as a function of group and frequency

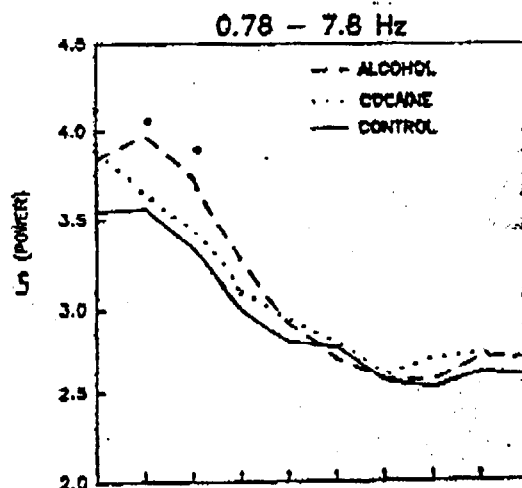
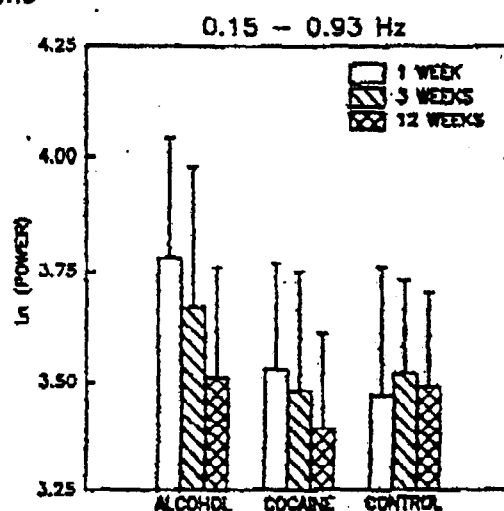


Fig. 5. Average action tremor amplitude from 0.15 to 0.93 Hz as a function of group and time



to the literature. For many years, investigators have attributed the ataxic gait and stance of alcoholics to cerebellar degeneration (Skillicorn, 1958; Victor et al., 1959; Silvuerskiold, 1977; Nieman et al., 1990). Our findings of enhanced body sway in recovering alcohol-dependent patients can be interpreted within this framework. Of course, one cannot exclude either myopathy or peripheral neuropathy as an alternative explanation (Scholz et al., 1986; Peudergast et al., 1990). The young age and relatively good medical health of our patient sample, however, argue against both as significant contributory factors.

The elevated action tremor found in alcohol-dependent patients is likewise consistent with cerebellar dysfunction. The task used to elicit action tremor required rapid ballistic pointing movements alternating with periods of sustained posture. Thus, the amount of tremor recorded during the task was actually a combination of true action tremor and tremor of the postural type. Both types of tremor have previously been reported in alcoholics (Koller et al., 1985; Carrie, 1965) and in patients with known cerebellar pathology (Gilman et al., 1981).

It is important to recognize that no differences were found between the alcohol-dependent group and the normal control group with respect to amount of normal physiologic tremor (Young, 1984), defined by its typical frequency range (i.e., 7-9 Hz). The group differences found during the pointing task are therefore probably unrelated to enhanced adrenergic outflow, anxiety, fatigue, or other benign processes that are believed to be indexed by physiological tremor. The absence of a group difference in physiologic tremor further reinforces the cerebellar hypothesis.

The present study was the first to conduct a systematic examination of tremor and body sway in a group of carefully diagnosed cocaine-dependent patients. As we noted previously, the only abnormality found in this group was an enhanced resting tremor, which did not diminish over the first 12 weeks of cocaine abstinence. The tremor was subtle and only detectable through the use of sensitive recording devices.

Nonetheless, an analogy can be drawn between the mild resting tremor found in the cocaine-dependent group and the more severe resting tremor found in patients with Parkinson's disease. This analogy is supported by the report by Volkow et al. (1991) of abnormal glucose utilization in the basal ganglia of abstinent cocaine abusers and by other studies that provide evidence for decreased dopaminergic tone in this population (Dackis and Gold, 1985; Kumor et al., 1986). It remains to be seen whether the subclinical movement disorder demonstrated presently will reach a level of clinical significance as abstinent cocaine abusers enter middle age or senescence. Yet it may already be significant for the subset of cocaine abusers whose occupations require fine or precise motor control, or rapid motor responses (cf. Roberts and Bauer, 1993).

Acknowledgments. This research was supported, in part, by NIDA grant RO1-DA05826 and NIAAA grant P50-AA3510.

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